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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/771,821	DOLITZKY ET AL.	
	Examiner	Art Unit	
	Anthony J. Paviglianiti	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-28 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 4-6 and 22-24 ~~is/are allowed~~. are allowable over the prior art of record. AJP

6)☒ Claim(s) 1,2,7-21 and 25-28 is/are rejected.

7)☒ Claim(s) 3 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 – 28 are currently pending in the application.

Priority

This application claims benefit of priority to Provisional Application No. 60/444,550 (filing date February 3, 2003) and Provisional Application No. 60/475,453 (filing date March 19, 2003).

Information Disclosure Statement

The Information Disclosure Statements (IDS) submitted on August 20, 2004, and September 20, 2004, are in compliance with the provisions of 37 C.F.R. §1.97, and both Information Disclosure Statements were considered by the examiner.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 2 and **25** are rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent 4,837,223 (issued June 6, 1989) to Jean Gobert, et al.

Specifically, **Claim 2** of the present invention claims "A process for preparing (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide which comprises cyclizing (S)-N—[1-(aminocarbonyl) propyl]-4-chlorobutanamide, in a solvent selected from the group consisting of acetonitrile and methyl tertbutyl ether, in the presence of a strong base, and recovering the crude levetiracetam." **Claim 25** recites, "Levetiracetam made by the process of any of claims 1 – 24."

The prior art, U.S. Patent 4,837,223 (Gobert) discloses "(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide substantially free of (R)-alpha-ethyl-2-oxo-1-pyrrolidinacetamide, prepared by the process which comprises cyclizing, in an inert solvent and in the presence of a basic substance, an (S)-2-aminobutanamide of the formula $X\text{-}CH_2CH_2\text{-}Y\text{-}NHCH(C_2H_5)CONH_2$, in which X represents ZOOC or $HalCH_2$-, wherein Z is alkyl of 1 to 4 carbon atoms and Hal a halogen atom, and Y represents $-CH_2-$ or –CO-..." (col. 10, lines 19 – 35, "claim 2").

The Specification for the prior art describes one specific compound of formula $X\text{-}CH_2CH_2\text{-}Y\text{-}NHCH(C_2H_5)CONH_2$ as "(S)-N-[1-(aminocarbonyl)propyl]-4-halobutanamide" (U.S. Patent 4,837,223 at col. 2, lines 57-65), which anticipates the (S)-N—[1-(aminocarbonyl) propyl]-4-chlorobutanamide which is cyclized in **Claim 2** of the present invention.

The present invention describes "acetonitrile" and "methyl tertbutyl ether" as "inert solvents." See Specification at page 3, lines 7 – 8. The present invention describes "strong base" as "preferably sodium hydroxide or potassium hydroxide." Id. at p. 3, lines 9 – 10. Likewise, the prior art defines the inorganic base used in the cyclization process as "potassium carbonate or hydroxide or sodium carbonate or hydroxide." See U.S. Patent 4,837,223 at col. 3, lines 5 – 6.

The prior art in Gobert therefore anticipates all of the limitations of **Claim 2**.

Claim 25, which claims the end-product, levetiracetam, "made by the process of **any of claims 1 – 24**" [emphasis added], is therefore also anticipated by U.S. Patent 4,837,223, and is rejected under 35 U.S.C. §102(b), because the "cyclizing" process of making levetiracetam described in **Claim 2** was previously disclosed in Gobert, *supra*.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 4,696,943 ("Gobert I").

Claims 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, and **21** are also rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 4,696,943 ("Gobert I")

Claims 26, 27, and **28** are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 4,837,223 ("Gobert II").

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Applying the "Graham" factors to Claim 1:

Determining the scope and contents of the prior art

Claim 1 of the present invention discloses, "A process for preparing (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide (levetiracetam) *comprising* reacting (S)-2-amino-butanamide hydrochloride and 4-chlorobutryl chloride in a solvent selected from the group consisting of

acetonitrile and methyl tertbutyl ether, in the presence of a strong base, and recovering the crude levetiracetam." [emphasis added].

The prior art, U.S. Patent 4,696,943 (Gobert I), discloses a process by which crude levetiracetam is produced from the very same reactants as in the present invention. See "Gobert I" at col. 6, lines 3 – 32, "Example 4." Gobert teaches that a suspension of (S)-2-amino-butanamide in CH_2Cl_2, to which anhydrous sodium sulfate [a drying agent] is added, cooling to 0° C., to which was added KOH and tetrabutylammonium bromide; then the second reactant, 4-chlorobutryl chloride, in a solution of CH_2Cl_2, was added slowly at 0° C., filtered, evaporated, and recrystallized in ethyl acetate to form the desired product, (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide (levetiracetam), with MP: 117° and 74.1% yield. U.S. Patent 4,696,943 col. 6, lines 5 – 34.

Ascertaining the differences between the prior art and the claims at issue

The present invention uses the inert solvents acetonitrile or methyl t-butyl ether for the production of levetiracetam, while the prior art reference uses the inert solvent CH_2Cl_2 (dichloromethane). Elsewhere in the prior reference, however, this same reaction is said to be generally carried out "in an inert solvent, such as benzene, toluene, dichloromethane or *acetonitrile*." [emphasis added] (Id. at col. 2, lines 63 – 67). In fact, the prior art provides an example where levetiracetam is produced from the same two starting reagents using acetonitrile as the solvent. See U.S. Patent 4,696,943 at col. 5, lines 24 – 32, "Example 3." [Note: Example 3 was not cited as a reference under this section because, unlike the present invention, the prior art described an intermediate compound, which was isolated, and then "cyclized" into the same desired end-product as the present invention. The intermediate, (S)-N-[1-aminocarbonyl)

propyl]-4-chlorobutanamide, is the same compound as disclosed in **Claim 2** of the present invention, which is cyclized into the end-product].

Another difference is the use of "tetrabutylammonium bromide" is disclosed in the process described by the prior art reference. The prior reference discloses that:

> "This cyclization [from the intermediate to the final product] is advantageously carried out in the presence of a *basic substance as a catalyst*. This catalyst is preferably... tetrabutyl-ammonium bromide when [one of the reactants] is a halide." [emphasis added] Id. at col. 2, lines 39 – 44.

Although the present invention expressly does not employ tetrabutylammonium bromide as a "catalyst" in the reaction, the present invention is conducted in the presence of a "basic substance" (powdered KOH). The yields of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide reported in the present invention (70% and 72%) are very nearly the same as disclosed in the prior art (74%). Id. at col. 6, line 44.

Resolving the level of ordinary skill in the pertinent art

Claim 1 simply recites the process for preparing crude levetiracetam from two reactants, (S)-2-amino-butanamide hydrochloride and 4-chlorobutryl chloride, in either acetonitrile or methyl tertbutyl ether, in the presence of a strong base. The prior art, Gobert, anticipates each of the stated limitations of **Claim 1** where the "strong base" is KOH, but the "solvent" is CH_2Cl_2 instead of acetonitrile or methyl tertbutyl ether. The resulting end-products are the same and produced in nearly the same yield. It would be obvious to a person skilled in the art that the inert solvents, methyl tertbutyl ether or acetonitrile, could be substituted instead of CH_2Cl_2, especially where the prior art had disclosed that this reaction is "generally carried out in an inert solvent, such as benzene, toluene, *dichloromethane or acetonitrile*." [emphasis added] (col. 2, lines 65 – 67). The skilled artisan would have been motivated to substitute acetonitrile instead of CH_2Cl_2

as the solvent for this reaction because the prior art already disclosed it as an option with a reasonable expectation of success.

Based on these factors, **Claim 1** of the present invention would have been obvious to one of skill in the art over U.S. Patent 4,696,943.

Applying the "Graham" factors to Claims 7 – 21:

Determining the scope and contents of the prior art

Briefly, **Claims 7** and **8** of the present invention add limitations concerning the maximum level of impurities in the end-product, levetiracetam, as measured in "% weight." **Claims 9, 10, 16, 17** and **18** of the present invention add limitations concerning recrystallization of the end-product, levetiracetam, with various organic solvent(s), to purify the product. **Claim 11** adds limitations on the relative molar concentrations of the strong base (e.g., KOH) and the reactant (S)-2-amino-butanamide hydrochloride. **Claims 12** and **14** add limitations on reaction temperatures. **Claims 13, 14, 19, 20** and **21** add limitations for the various drying agents.

The prior art teaches that the "optical purity" of the end-product (i.e., the proportion of (S)- and (R)-isomers) was verified by "calorimetric determination of the differential enthalpies," (col. 3, lines 18 – 21), but does not expressly state the purity of levetiracetam as measured in either "% weight of impurities" or "% weight of the (R)-isomer."

The prior art discloses that the end-product, levetiracetam, is "recrystallized in ethyl acetate" in the presence of a powdered drying agent (molecular sieve). (Gobert at col. 4, line 21; col. 5, lines 17 and 65; and col. 6, line 27).

The prior art does not state a specific "molar ratio" between the amount of strong base and the amount of reactant (S)-2-amino-butanamide hydrochloride, but does provide the amounts used of each, measured in grams, from which the ratio could be calculated.

The prior art discloses temperatures for various steps of the reaction. See, e.g., col. 4, lines 8 and 10; col. 5, lines 8, 55, 58, and 61; and col. 6, lines 13, 18, and 23.

The prior art discloses various drying agents used to produce levetiracetam and to aid in recrystallization. See, e.g., col. 5, lines 66 (powdered molecular sieve); col. 6, line 11 (anhydrous Na_2SO_4) and line 28 (molecular sieve).

Ascertaining the differences between the prior art and the claims at issue

Claims 7 and **8** of the present invention are dependent upon **Claim 1**, adding the limitation on the end-product that it contain "less than about 0.4% by weight of [the (R) isomer]," and "less than 0.2% by weight of impurities" respectively. By comparison, the prior art, U.S. Patent 4,696,943 (Gobert I), teaches that the "optical purity" of the end-product (i.e., the proportion of (S) and (R) isomers) was verified by "calorimetric determination of the differential enthalpies," (col. 3, lines 18 – 21), but does not state the purity of levetiracetam as measured in either "% weight of impurities" or "% weight of the (R) isomer."

Claims 9, 10, 16, 17 and **18** are directly or indirectly dependent upon **Claim 1**, adding an additional process step where the end-product, levetiracetam, is purified by recrystallization with various organic solvent(s). By comparison, the prior art discloses that the end-product, levetiracetam, is "recrystallized in ethyl acetate" in the presence of a powdered drying agent (molecular sieve). (Gobert at col. 4, line 21; col. 5, lines 17 and 65; and col. 6, line 27).

Claim 11 is dependent upon **Claim 1**, adding the limitation on the relative molar concentrations of the strong base (e.g., KOH) and the reactant (S)-2-amino-butanamide hydrochloride. By comparison, the prior art does not state a specific "molar ratio" between the amount of strong base and the amount of reactant (S)-2-amino-butanamide hydrochloride, but does provide the amounts used of each, measured in grams, from which the ratio could be calculated.

Claims 12 and **14** are directly or indirectly dependent upon **Claim 1**, adding limitations on reaction temperatures. In comparison, the prior art discloses temperatures for various steps of the reaction. See, e.g., col. 4, lines 8 and 10; col. 5, lines 8, 55, 58, and 61; and col. 6, lines 13, 18, and 23.

Claims 13, 14, 19, 20 and **21** are directly or indirectly dependent upon **Claim 1**, adding limitations for the various drying agents. By means of comparison, the prior art discloses various drying agents used to produce levetiracetam and to aid in recrystallization. See, e.g., col. 5, lines 66 (powdered molecular sieve); col. 6, line 11 (anhydrous Na_2SO_4) and line 28 (powdered molecular sieve).

Resolving the level of ordinary skill in the pertinent art

Based on the prior art, "Gobert I," it would have been obvious to a person of skill in the art at the time of the application to prepare the desired product, (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide (levetiracetam), by controlling those factors which are claimed in **Claims 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,** and **21**: that is, to prepare levetiracetam to a level of purity to less than a certain "% by weight of impurities" (**Claims 7** and **8**); to

recrystallize the final product to increase its purity (**Claims 9, 10, 16, 17** and **18**); to use drying agents such as molecular sieves or sodium sulfate (**Claims 13, 14, 19, 20** and **21**).

Based on these factors, **Claims 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,** and **21** of the present invention would have been obvious to a skilled artisan over U.S. Patent 4,696,943.

Applying the "Graham" factors to Claims 26 – 28:

Determining the scope and contents of the prior art

Claim 26 recites, "A pharmaceutical composition comprising the product of claim 25 and a pharmaceutically acceptable carrier." **Claim 27** recites, "A pharmaceutical formulation comprising levetiracetam and a pharmaceutically acceptable carrier, wherein the formulation comprises less than 0.2% by weight of impurities." **Claim 28** recites, "The pharmaceutical formulation of claim 27, wherein the formulation comprises less than 0.1% by weight of impurities."

The prior art, U.S. Patent 4,837,223, discloses "A pharmaceutical composition comprising a pharmaceutically effective amount of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide and a pharmaceutically acceptable sold or liquid diluent or carrier therefor, said composition being substantially free of (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide." (col. 10, lines 13 – 18, "claim 1").

Claims 26 – 28 of the present invention and the prior art both disclose a pharmaceutical composition (or "formulation") of the desired (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide compound and a "pharmaceutically acceptable carrier." See U.S. Patent 4,837,223 at col. 9,

lines 27-28 and col. 10 at lines 13 – 16 (prior art) and **Claims 26 – 28**, page 7, lines 3 – 9 of amended claims (present invention).

The prior art discloses that the desired product, (S)-α-ethyl-2-oxo-1-pyrrolidine-acetamide, is recrystallized in the organic solvent, ethyl acetate (See, e.g., col. 5, line 24-26 and col. 6, lines 4 – 6), as a method of purifying the product, but does not quantify the level of impurities by weight achieved.

Ascertaining the differences between the prior art and the claims at issue

Unlike the present invention, claim 1 in the prior art does not quantify precisely what "substantially free" [of (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide] means, while the present invention quantifies the level of "impurities" (i.e., the unwanted (R) isomer, or alternatively, unwanted chemical impurities) as "less than 0.2% by weight" **(Claim 27)** and "less than 0.1% by weight" **(Claim 28)**. The present invention defines "purity" by weight in terms of both "optical purity" (Specification at page 4, line 9) and "chemical purity" (Id. at line 12). In the context of this analysis, it is not certain which of the two meanings for "impurities" is intended in **Claims 27** and **28**.

The "optical purity" of the recrystallized products was measured by different tests: in the prior art, by "calorimetric determination of differential enthalpies" (col. 3, lines 21 – 24) and, in the present invention, "chiral capillary GC" (Specification at page 10, lines 12 – 13).

Resolving the level of ordinary skill in the pertinent art

It would have been obvious to one of skill in the art to prepare "purified" forms of the product, (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide, where the intended use of the product was as

a composition used as a medication for seizures in adults with epilepsy. See Specification at page 1, lines 14-15.

The present invention and the prior art both use recrystallization in an organic solvent (such as ethyl acetate) as a method of purifying the crude levetiracetam produced in the initial reaction. Compare U.S. Patent 4,837,223 at col. 5, line 24-26 and col. 6, lines 4 – 6 with **Claims 9** and **10** of the present invention.

A person skilled in the art would have been motivated to prepare a compound which was both "optically pure" (i.e., free from the unwanted (R)-isomer) as well as "chemically pure" (i.e., free from common impurities), because it was known in the art at the time of the application that the (S)-isomer of etiracetam [the racemic mixture of levetiracetam and its (R)-isomer] had 10 times higher protective activity against hypoxia and 4 times higher protective activity against ischemia than the racemic form. See U.S. Patent 4,837,223 at col. 1, lines 27 – 35. Therefore, a skilled artisan would have a reasonable expectation of success that, by increasing the chemical and optical purity of the compound, the effectiveness of the compound would be improved without a corresponding increase in the likelihood of adverse effects.

Given these factors, the recrystallized (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide in the prior art, which was claimed to be "substantially free" of (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide (col. 10, line 18), as verified by calorimetric determination of differential enthalpies (U.S. Patent 4,837,223 at col. 3, lines 21 – 24) would have been of the same or similar optical purity as was found for the recrystallized product claimed in the present invention, where the level of optical impurity was measured by chiral capillary GC (Specification at page 10, lines 12 – 13).

Based on all of these factors, **Claims 26 – 28** of the present invention would have been obvious to one of skill in the art over U.S. Patent 4,837,223.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 27 and **28** are also rejected under 35 U.S.C. §112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, **Claims 8, 27** and **28** each refer to "less than 0.2% [or 0.1%] by weight of impurities." However, the Specification expressly describes two different types of "impurities": namely, "optical purity" (page 4, line 9) and "chemical purity" (page 4, line 12). The Specification discloses *both* types of purity as being measured as "% by weight." The use of the word "impurities" in these three claims renders **Claims 8, 27** and **28** vague and indefinite.

The foregoing rejection may be obviated by adding the word "optical" or "chemical" (or both) before the word "impurities" in Claims 8, 27 and 28.

Claims 17, 18 and **19** are also rejected under 35 U.S.C. §112, second paragraph, because the claims do not refer to a preceding claim. MPEP §608.01. Specifically:

> **Claim 17** recites, "The process of claim 17...";
> **Claim 18** recites, "The process of claim 18..."; and
> **Claim 19** recites, "The process of claim 19..."

These rejections may be obviated by amending Claims 17, 18 and 19 to refer to a *preceding* claim, such as "The process of claim 16..." "The process of claim 17..." and "The process of claim 14...," respectively.

Claim Objections

Claim 3 is objected to for being dependent upon a rejected base claim, but appears to be free of the prior art of record if rewritten in independent form including all of the limitations of the base claim and any intervening claims. See MPEP §608.01(n)(V).

ANALYSIS OF CLAIMS 4 – 6, AND 22 – 24

Claim 4, which recites, "A process for preparing (S)-α-ethyl-2-oxo-1-pyrrolidine-acetamide (levetiracetam) comprising reacting (S)-2-amino-butanamide hydrochloride and 4-chlorobutryl chloride, in an inert solvent, *in the absence of a catalyst*, and recovering the crude levetiracetam" [emphasis added], appears to be free of the prior art of record because of the limitation of "in the absence of a catalyst." Although the process of preparing this particular end-product from these two particular reactants is not novel, in itself, doing so "in the absence of a catalyst" appears to be free of prior art. The closest prior references, the two Gobert patents cited above, and the British patent application GB 2 225 322 A (published May 30, 1990), do not disclose a process for making levetiracetam from these particular reactants in the absence of a catalyst; therefore, there appears to be no prior art reference which meets all of the limitations of **Claim 4** or makes them obvious.

Claims 5 and **6**, which are dependent on **Claim 4**, also appear to be free of the prior art. The closest art appears would be the two Gobert patents, for the reasons given for Claim 4, above.

Claims 22, 23 and **24**, which are directly or indirectly dependent upon **Claim 1**, add limitations of adding an acid (or mixture of acids) to adjust the pH of the "completed" reaction mixture. The preparation of levetiracetam in the Gobert patents, by contrast, does not appear to

include the step adding acid(s) to adjust the pH after the reaction is completed (though Gobert does cite an alternative method of preparing levetiracetam where hydrochloric acid is added to make the starting material, (±)-ethyl-2-oxo-1-pyrrolidineacetic acid at col. 4, lines 48-50). Although the present invention did not disclose a specific purpose for adding a mixture of acids to adjust the pH of the completed reaction (see Specification at p. 3, lines 29 – 31), there appears to be no prior art reference which meets all of the limitations of **Clams 22, 23** or **24**, or makes them obvious over the prior art.

Conclusion

Claims 2 and **25** were rejected under 35 U.S.C. §102(b).

Claims 1, 7 – 21, and **26 – 28** were rejected under 35 U.S.C. §103(a).

Claims 8, 17, 18, 19, 27 and **28** were rejected under 35 U.S.C. §112, 2nd paragraph.

Claim 3 was objected to as being dependent upon a rejected base claim.

Claims 4 – 6 and **22 – 24** appear to be free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Anthony J. Paviglianiti** whose telephone number is **(571) 272-3107**. The examiner can normally be reached on Monday-Friday, 8:30 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached at (571) 272-0699. The FAX phone number for the organization where this application or proceeding is assigned is (571) 273-8300. **Please note that this is a new central FAX number for official correspondence.**

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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